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Comparison of Novel Strategy Therapies for Obstructive Hypertrophic Cardiomyopathy: Relation of Relief of Left Ventricular Outflow Obstruction to Improved Symptoms and Health-Related Quality of Life Parameters

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Background: Left ventricular (LV) outflow obstruction is present in about a third of patients with hypertrophic cardiomyopathy (HCM), and may cause disabling symptoms. Alcohol septal ablation (ASA) and dual chamber (DDD) pacing have been proposed as alternative therapies to cardiac surgery for relief of LV outflow obstruction. **Methods:** We compared the impact of ASA and DDD on LV gradient, symptoms and health-related quality of life (HRQL) in a randomized prospective study involving 70 patients with obstructive HCM and drug-refractory symptoms. The demographic and clinical characteristics of the 2 arms were similar. Patients completed the SF-36 Health Survey and a symptom measure at baseline (prior to randomization), 3 and 6 months. **Results:** Both procedures significantly reduced the LV outflow gradients determined at cardiac catheterization: ASA arm, the mean (SD) gradient reduced from 105 (32) mm Hg to 33 (32) mm Hg [a change of 72 (37) mm Hg, or 69%; and DDD arm, from 101 (36) mmHg to 49 (39) mm Hg (a change of 51 (32) mm Hg, or 50%]. ASA resulted in significantly (about 20 mm Hg) greater reduction in LV gradient, $p=0.017$. Of the 70 patients randomized, 32 DDD and 29 ASA were available for HRQL analysis. Both therapies resulted in significant and equal improvement in all symptom and HRQL outcomes from baseline to 3 months, with no further change at 6-month follow-up. There was no significant correlation between changes in symptoms or HRQL and reductions in LV gradients, perhaps due to the dynamic nature of the LV outflow obstruction. **Conclusions:** (1) ASA and DDD are both effective in relieving LV obstruction in most patients; and 2) both DDD and ASA are associated with significant symptom and HRQL benefits at 3 months that persist to 6 months. As the symptomatic and HRQL benefits were equivalent, DDD pacing should perhaps be tried first. ASA may then be performed in patients with residual obstruction and symptoms without concerns about inducing heart block.

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Septal Ablation for Symptomatic Hypertrophic Obstructive Cardiomyopathy: An Analysis of the Patients With Dissatisfactory Intervention Results

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Background: In 90% of the patients (pts.) with symptomatic hypertrophic obstructive cardiomyopathy (HOCM) the outflow gradient (LVOTG) can significantly be reduced or removed by septal ablation (PTSMA). Pts. with a dissatisfactory LVOTG response are not yet characterized sufficiently.

Results: From 279 pts. re-evaluated 3 months after PTSMA, 36 (13%) had PTSMA failure (PF) defined as a less than 50% LVOTG reduction. On average, these pts. were younger (50 ± 18 vs. 54 ± 14 years; $p < 0.01$), had a thicker septum (22.4 ± 1 vs. 20.4 ± 1 mm; $p < 0.05$), a higher baseline LVOTG (69 ± 33 vs. 58 ± 33 mm Hg; $p < 0.01$), and a lower CK release after PTSMA (477 ± 228 vs. 556 ± 272 U/l; $p < 0.05$).

The main cause for PF was an insufficient PTSMA lesion on 2D-echo at follow-up ($n=22$; successful re-PTSMA in 6 pts., surgery in 1 pt. and spontaneous LVOTG reduction in 8 pts. within the following 12 months). Suboptimal scar localization, observed in 7 pts. treated before routine echocardiographic guidance (MCE) for PTSMA and requiring a re-PTSMA in 4 pts. and surgery in 2 pt., was not seen with MCE-guidance any more.

Another group of pts. with PF showed persisting SAM and LVOTG despite a sufficient PTSMA scar due to excessive elongation of the mitral leaflets ($n=5$; spontaneous LVOTG elimination in one of them within 12 months). One pt. each had coexistent fibromuscular subaortic stenosis and severe midcavity obstruction which both did not respond to PTSMA.

Conclusions: Even with MCE guiding, younger pts. with a thicker septum, and those with markedly elongated mitral leaflets seem to be less suitable for PTSMA. Furthermore, LVOTG elimination may need up to 1 year. Pre-interventional pt. selection, echocardiographic assessment, and pt. information should take these findings into consideration.

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Prevalence and Spectrum of Thin Filament Mutations in Patients With Hypertrophic Cardiomyopathy: A Comprehensive Mutational Analysis of Troponin T, Troponin I, Alpha Tropomyosin, and Cardiac Actin

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Background: Thin filament mutations are reported to cause ~20% of Hypertrophic Cardiomyopathy (HCM) and display a diverse phenotype. However, the frequency of these mutations and their associated phenotype in a single large cohort have not been reported. We determined the prevalence and spectrum of mutations in the genes encoding the thin filament proteins cardiac troponin T (*TNNI2*), cardiac troponin I (*TNNI3*), alpha tropomyosin (*TPM1*), and cardiac actin (*ACTC*) in a large cohort of unrelated HCM patients, and searched for defining clinical characteristics for thin filament-HCM.

Methods: DNA from 395 unrelated patients with HCM was obtained and analyzed. Mutational analysis of all protein coding exons of *TNNI2* (15 exons), *TNNI3* (8), *TPM1* (9), and *ACTC* (6) was performed using polymerase chain reaction, denaturing high performance liquid chromatography, and DNA sequencing. The clinical data were maintained in a database independent of the patient genotype.

Results: Overall, only 19 patients (4.8%) were identified having 12 distinct thin filament mutations: 9 with *TNNI2* mutations, 6 with *TNNI3* mutations, 3 with *TPM1* mutations, and 1 with an *ACTC* mutation. Of the 12 unique missense mutations identified, 8 (67%) were novel mutations. As a group, patients with thin filament mutations were not significantly different from the rest of the cohort in age at diagnosis, left ventricular wall thickness (LVWT), gradient, or family history of HCM or sudden death. However, when compared to patients with beta myosin heavy chain mutations ($n=54$), patients with thin filament mutations had less hypertrophy (LVWT = 19.8 ± 6 mm versus 24.3 ± 8 mm, $p = 0.04$).

Conclusions: This study represents a comprehensive evaluation for mutations in the genes encoding the thin filament of the cardiac sarcomere at a large, tertiary referral center for HCM. Here, thin filament mutations were identified in <5% of the HCM cohort. Moreover, except for a lesser degree of hypertrophy when compared to patients with thick filament HCM on the basis of mutations in the beta myosin heavy chain, there were no clinical features to distinguish this small subset of thin filament-HCM from HCM due to mutations in other genes.

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Evidence That Left Ventricular Outflow Tract Obstruction Is a Predictor of Outcome in Patients With Hypertrophic Cardiomyopathy

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Background: One of the most visible and quantifiable features of hypertrophic cardiomyopathy (HCM) has been the left ventricular (LV) outflow tract gradient. Major therapeutic interventions (such as surgery, alcohol septal ablation and pacing) have been introduced to relieve subaortic obstruction and disabling symptoms. However, the significance of LV outflow obstruction with regard to clinical outcome in HCM has been the subject of controversy and remains incompletely unresolved.

Methods: We assessed the impact of LV outflow gradient on mortality and morbidity in a large HCM cohort prospectively followed over 6.3 ± 6.2 years.

Results: Of 1101 consecutive patients, 127 (12%) died of HCM and 196 (18%) developed severe progressive heart failure-related symptoms (NYHA functional classes III/IV); at initial evaluation, 273 study patients (25%) had LV outflow obstruction under basal conditions with continuous wave Doppler (gradient, ≥ 30 mm Hg). Probability of HCM-related mortality and progression to severe disabling symptoms was significantly greater in patients with outflow obstruction than in those without (OR 2.0 and 4.4, respectively; $p < 0.0001$ for both end-points), and was most substantial in obstructive patients ≥ 40 years old ($p < 0.001$). HCM mortality and morbidity due to obstruction did not increase with greater magnitude of gradient above the threshold of 30 mm Hg. Multivariate analysis showed outflow obstruction to be a strong and independent predictor of HCM-mortality and severe symptoms (OR 1.6; $p=0.018$) among several other disease variables. Likelihood of sudden death was also greater in patients with obstruction (OR 1.9; $p=0.014$), although the positive predictive value for obstruction was low (i.e., only 7%).

Conclusions: Basal LV outflow obstruction (gradient, ≥ 30 mm Hg) is a strong and independent predictor of progression to severe symptoms and cardiovascular mortality in HCM. Therefore, treatment interventions that reduce outflow gradients can be expected to favorably influence quality of life and long-term prognosis in severely symptomatic patients with obstructive HCM, and could possibly be justified somewhat earlier at lesser gradients than is current practice.

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Left Atrial Volumetric Remodeling Predicts Functional Capacity in Hypertrophic Cardiomyopathy

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Background: Left atrial volumetric remodeling (LAR) is a marker of hypertensive left ventricular (LV) hypertrophy and associated cardiovascular events and probably represents chronic hemodynamic overload. Its role as an indicator of disease severity in primary hypertrophic cardiomyopathy (HCM) has not been reported. We, therefore, compared the association of two-dimensional echocardiographically-determined LAR and other structural and hemodynamic parameters with objective measures of exercise functional capacity in 26 patients (14 males, 12 females, mean age=37 years).

Methods: BSA-normalized left atrial volume by modified Simpson's biplane method, M-mode (MM) and trans-mitral Doppler (E/A ratio) echocardiographic measures were obtained in patients undergoing cardiac catheterization within 24 hours of echocardiographic assessment and correlated with metabolic treadmill stress testing performed during the same admission. Magnetic resonance imaging (MRI)-determined LV mass was also obtained in a subset of 13 subjects.

Conclusions: Volumetric LAR in HCM patients correlated significantly and consistently with metabolic stress testing parameters. LAR predicted objective functional capacity at least as well as resting invasive hemodynamic assessment and was superior to other forms of echocardiographic and MRI LV mass assessment.